Botanicals and Nutrients to Address Mood Disorders and Depression

Co-authored by Donald R. Yance, RH (AHG), CN and Suzanne E. Sky, L.Ac., MTOM

Discussion

MOOD DISORDERS AND DEPRESSION

Mood disorders, such as depression and anxiety, persistently affect a person's mental/emotional state and adversely influence their daily life. Anxiety and depression are often concurrent along with impaired sleep and cognitive function. These conditions may be triggered by a variety of factors including nutritional, psychological, biochemical, emotional, environmental, social and spiritual. Cognitive, mood and sleep disorders hamper our ability to lead vibrant, healthy lives and to respond appropriately to the many challenges of life.

In 2012, according to the National Institute of Mental Health (NIMH), major depression is one of the most common mental disorders in the United States[1] affecting about 6.9% of adults. Worldwide, depression impacts about 17% of people.[2] Women are 70% more likely to experience depression.[3] Findings show that 11% of Americans aged 12 years and older take antidepressant medication. Twenty-three percent of women age 40 to 49 take antidepressants, more than in other age groups.[4]

While most of us experience some degree of depression in our lives, for many people this is a chronic and even debilitating condition. Some estimates predict that by 2020 depression could be a major disease, second only to cardiac ischemia.[5] Depression is a wide field of study and it is currently hypothesized that there are many types of depression governed by genetic, gender, cultural and biochemical variations.[6]

BRAIN HEALTH: BOTANICALS AND NUTRIENTS

Even with decades of burgeoning research, we are still discovering the complexity of the brain, its function and its relation to our health, mood and cognitive ability. Nutrition and dietary factors play a huge role in our neurological health because they influence cellular health and neurotransmitter production. Our emotions and mood are intrinsically interconnected with the production, relay and inhibition of specific neurotransmitters. The biochemical model considers depression as most often resulting from deficiency or dysfunction of neurotransmitters in either the catecholamine (CA) or indoleamine (IA) systems.

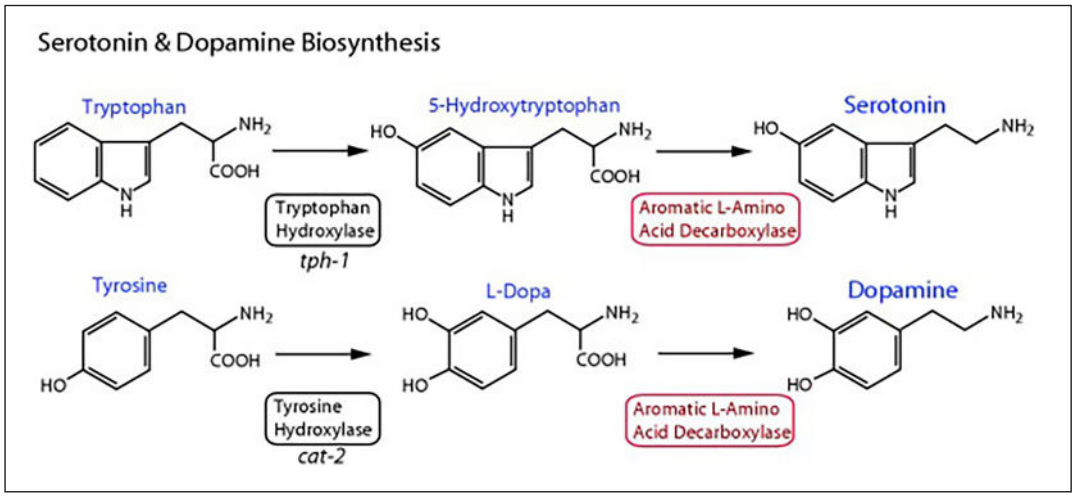
The CA system involves norepinephrine and requires the precursors tyrosine and DOPA (dihydroxyphenylanine). Compounds of the IA system include serotonin (5-hydroxytriptamine or 5-HT). Its precursors include tryptophan and 5-HTP (5-hydroxytryptophan).[7] Studies find that these precursors are found abundantly in botanicals and nutrients that also modulate a healthy balance of neurotransmitters and enhance cellular and neuroendocrine function.

There are over forty years of scientific reviews and research on the health-promoting potential of botanicals.[6] Botanical medicines offer a profound alternative and adjunct to pharmaceutical medicines, especially when used in combination with nutrients and natural compounds to support foundational issues and optimize cognition and mood.

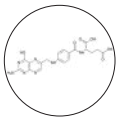
Botanicals and nutrients are powerful because they address the root cause of dysfunction. They help restore normal levels of neurotransmitters and harmonize the interface between the hormonal, immune and nervous systems. Thus, botanical and nutritional compounds play a supportive and sometimes central role in providing tangible relief in those with mild to moderate mood disorders. In more serious and chronic conditions, botanical and nutritional compounds can provide a beneficial adjunct to pharmaceutical medications. This is because they support underlying physiological functions at the cellular and neuroendocrine level.

Botanicals and natural compounds work on multiple levels to calm inflammatory pathways and modulate healthy response

to stress. For cognitive and mood disorders, botanicals and nutrients are chosen to restore HPA (hypothalamic-pituitary-adrenal) axis function, replenish depleted adrenal reserves and enhance cellular and neurotransmitter function. This contributes to positive cognition and mood, supports the individual to regain their natural allostatic and circadian rhythms and thus enhances wellness at all levels.



Source: Hare and Loer. *BMC Evolutionary Biology*. 2004. 4:24. doi:10.1186/1471-2148-4-24.

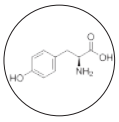


Naturized® Vitamins B6, B12, Folate

B-complex vitamins act as co-factors in enzyme reactions that facilitate numerous biochemical responses. Vitamins B6, B12 and folate are protective and nourishing for the nervous system. They play a key role in metabolic (energy-production) pathways at the cellular level. In addition, they support healthy function of the liver's methylation system, promoting healthy liver clearance and metabolic function. Studies indicate that elevated homocysteine results from inadequate folate, Vitamin B12 and B6 intake and correlates with cognitive impairment.[8]

Several members of the B-complex are precursors for the calming neurotransmitters. B6 and B12 are essential co-factors for neurotransmitter synthesis. B12 is shown to delay onset of dementia.[9] B12 and folate are found to support cognition and functional ability.[10] Low vitamin B12 levels can be a contributing factor to neuron atrophy and cognitive decline.[11] Vitamins B6 and folic acid are required to support the conversion of tyrosine into neurotransmitters.

Naturized® nutrients utilize a single-celled yeast, *Saccharomyces cerevisiae*, which is fed specific vitamins and minerals that in turn become extremely bioavailable through the yeast.



N-Acetyl-L-Tyrosine

The amino acid tyrosine is the precursor to L-dopa, dopamine, norepinephrine and epinephrine. The conversion of tyrosine into these neurotransmitters requires the vitamins B6, C and folic acid. Tyrosine is naturally found in animal proteins (fish, meat, dairy, eggs), soybeans, nuts, seeds, beans, dairy and whole grains. It is found that both carbohydrate and protein meals raise the serum tyrosine and brain tyrosine levels.[6]

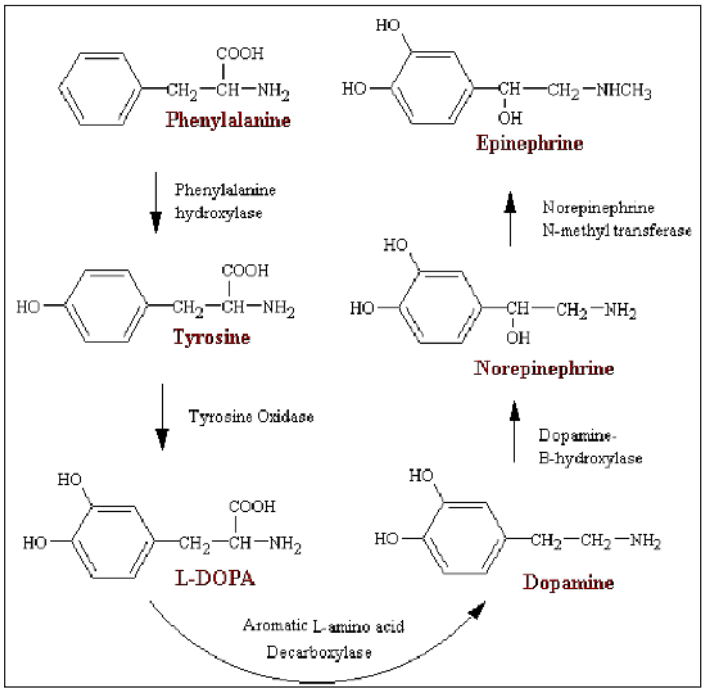
L-tyrosine is known as a conditionally essential amino acid because its normal pathways of synthesis from the essential amino acid L-phenylalanine can be impaired due to illness, trauma, liver disease or severe stress. Under these conditions of disrupted conversion, Tyrosine becomes an essential amino acid.

Tyrosine helps form the bioactive factors vital to cellular growth and maintenance. Tyrosine is a precursor to thyroid hormones and to a group of compounds known as catecholestrogens. These compounds exert estrogen- and catecholamine-like effects. Tyrosine is also involved in the synthesis of enkephalins, which are peptides in the endorphin family.

Tyrosine is precursor to the catecholamines influencing synthesis of dopamine, epinephrine and norepinephrine. It can support replenishment of the catecholamines when they are depleted due to stress. Tyrosine forms L-dopa (dihydroxyphenlalanine), which is converted to dopamine. Dopamine can be converted to norepinephrine and then to epinephrine.

The neurotransmitters norepinephrine (NE) and dopamine both play a role in depression.[6] Studies suggest that Tyrosine helps improve cognitive function and memory while under stress[12] and that it has potential as an antidepressant.[13] Tyrosine is found to enhance NE activity in the brains of animals.[13] Tyrosine enhances cognitive performance in short-term stressful situations such as those demanding high cognitive function in healthy subjects where there is a temporary depletion of dopamine and/or norepinephrine.[14,15] It is thought to facilitate cognitive resilience because it replenishes the neurotransmitters essential to clear cognition.[15]

Tyrosine is essential for the formation of thyroid hormone and is part of the molecular structure of thyroid hormones. Because the thyroid gland plays a key role in establishing the body's metabolic rate by directing mitochondrial energy production, Tyrosine is an essential part of energy production. Thyroid function also influences mood through its metabolic role.



Source: http://faculty.weber.edu/ewalker/Medicinal_Chemistry/topics/Adrenergic/adrenerg.htm

Practitioners often prefer to use N-Acetyl-L-Tyrosine because it is more stable than L-Tyrosine and offers much better absorption qualities through the digestive tract. N-Acetyl-L-Tyrosine is considered to exert its influence more specifically on the brain and neurotransmitters than other forms of Tyrosine.

St. John's Wort *(Hypericum perforatum)*

St. John's Wort, a plant that is indigenous to Europe, western Asia and North Africa, grows worldwide and is a common wayside weed in areas of North America. It is traditionally used for depressive disorders because of its beneficial effect on the nervous system. Hypericum extract is widely studied and highly regarded as a treatment for depression. Studies find that a dosage of 300 to 900 mg of the plant extract is significantly more effective than placebo and well-tolerated in cases of mild to moderate depression.[5,16,17]

According the 2008 Cochrane report, evidence suggests that Hypericum extracts are also superior to placebo in patients with major depression.[18] It is also found to be significantly superior to placebo when tested with an elderly population (over 60 years of age).[19]

Hypericum is extensively studied because scientists find it unique in many aspects such as its biochemical composition and its capacity as a whole plant to alleviate depression. The biochemistry of Hypericum offers such diversity and complexity that it is said to "display the pharmacology of many classes of antidepressants and new mechanisms not typical of standard antidepressants".[20] Many of its compounds exert a modulatory influence through multiple actions and pathways.[18,21] Studies report the extract of the whole plant to be the most efficacious form.[5,16,17,20,21]

Hypericum is known for its ability to normalize serotonin levels.[2] The plant contains flavonoids, xanthones, phenolic acids, terpenes, hypericin and hyperforin. It also contains indole compounds including a high concentration of melatonin. While researchers are still curious about the role of melatonin in plants, they theorize that, as in mammals, serotonin and melatonin act as modulator of circadian rhythms in the plant cycle.

In plants they are thought to mediate photoperiodic responses. In humans the serotonin/melatonin metabolites are well-known for their role in regulating circadian rhythms. While melatonin is found in several medicinal plants, St. John's Wort is found to have significant amounts.[5,21] These compounds also exert a protective, antioxidant capacity.[5,21]

Studies find that hyperforin inhibits reuptake of serotonin, adrenaline, noradrenaline, GABA and L-glutamate. The bioflavonoids and xanthones of the Hypericum plant extract are found to exert antidepressant influence.[5,20] Studies report that Hypericum plant extract is neuroprotective[5,16] and alleviates depression.[5] Recent studies suggest that St. John's Wort plays a role in regulating genes that control HPA axis function.[17]

Magnolia Bark *(Magnolia officinalis)*

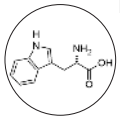
Magnolia Bark is highly-esteemed in the traditional medicines of China and Japan. The Japanese refer to it as *saiboku-to* and drink Magnolia Bark tea to alleviate anxiety. Magnolia demonstrates anti-stress benefits that allows adaptation to stress and modulates the stress-hormone cortisol.

Magnolia Bark is rich in many biologically-active compounds including alkaloids, coumarins, flavonoids, lignans and terpenoids.[29] One of Magnolia Bark's main constituents is honokiol, which is the most-researched bioactive constituent. This polyphenolic compound exhibits powerful antioxidative and anti-inflammatory activity. Up-Lift™ utilizes a Magnolia Bark extract standardized to 50% honokiol.

Many studies show that honokiol acts as a potent anti-stress agent. One study found honokiol to be five times stronger than diazepam in reducing anxiety with no side effects, although honokiol has no influence on muscle relaxation.[29] Honokiol exerts a highly neuroprotective influence. It is found to calm oxidative and inflammatory processes in neurons and microglial cells and has the ability to inhibit the NF-kB pathway.[30-32]

A combination of magnolol (another phenolic compound in Magnolia Bark) and honokiol was used in animal studies. Researchers find this mixture alleviates mild to moderate depression and normalizes HPA-axis hyperactivity.[33] Studies report that magnolol and honokiol exhibit neurotrophic function and help upregulate production of acetylcholine, which is essential for healthy brain function.[34] These compounds are both shown to enhance and modulate the activity of $GABA_A$ receptors and may inhibit glutamate receptors.[35]

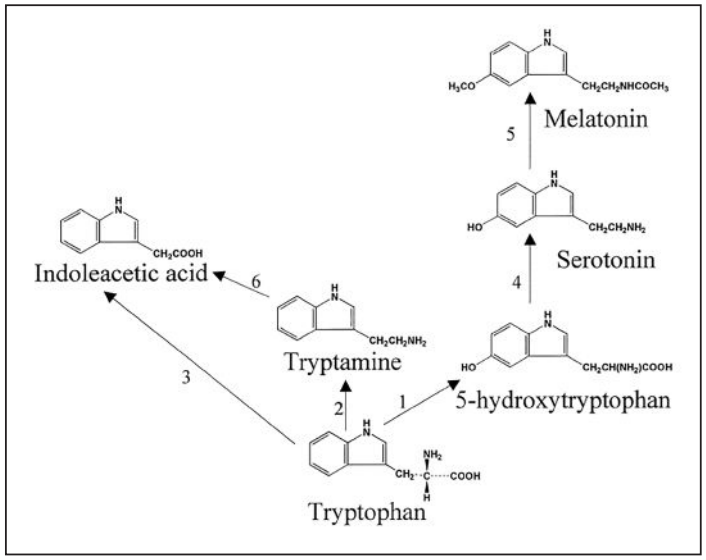
L-Tryptophan



Tryptophan plays a key role in formation of neurotransmitters. This essential amino acid, obtained from food, is the precursor to the neurotransmitters serotonin and melatonin, which play key roles in regulating mood, appetite and circadian rhythms. Dietary consumption of proteins exerts an influence on brain function and mood. Eating a meal high in carbohydrates is known to raise brain levels of both Tryptophan and 5HT.[6] Tryptophan is first converted to 5-HTP and then to serotonin (5-HT), which is the active neurotransmitter. Further, the

hormone melatonin is synthesized from serotonin in the pineal gland. Serotonin (5-HT) influences mood, sleep, metabolism, appetite and sexuality. Serotonin also modulates anger and aggression. Supplementation of Tryptophan is found to be beneficial in the management of neuropsychiatric disorders.[36]

Factors that inhibit tryptophan hydroxylase (the enzyme that facilitates conversion to Tryptophan) include stress, insulin resistance, deficiency of vitamin B6 or magnesium and high doses of Tryptophan.[6] Tryptophan easily crosses the blood-brain barrier. It is found most beneficial for those with mild to moderate depression.[6]



Source: Murch SJ, KrishnaRaj S, Saxena PK. *Tryptophan is a precursor for melatonin and serotonin biosynthesis in in vitro regenerated St. John's wort (Hypericum perforatum L. cv. Anthos) plants*. Plant Cell Reports 2000. 19:698-704.

Ashwagandha *(Withania somnifera)*

Ashwagandha or Winter Cherry, is a woody shrub in the Solanaceae family that grows in diverse areas including Africa, India and the Mediterranean.

This powerful herb has been revered in Ayurvedic medicine for over five thousand years. Often called Indian Ginseng, it belongs to an elite class of Ayurvedic restorative, tonic herbs, known as Rasayana. The name Ashwagandha means "the smell of a horse," referring to the strong smell of the root. It also refers to the traditional belief that Ashwagandha root confers the vigor, virility, and strength of a stallion.

The botanical name "somnifera" means "restful sleep". Botanicals classified as tonics in many traditional medicines most often act through what we would refer to in modern times as modulation of the HPA axis. Their tonic action is due to their normalizing action, particularly on the neuroendocrine system, rather than a stimulant effect. Stimulants overtax the nervous system while adaptogenic tonics such as Ashwagandha work by nourishing and thus enhancing relaxation of the nervous system. In Ayurvedic and Chinese medicine, it is understood that when our nervous system is functioning optimally, we can relax deeply and enjoy a truly restful sleep. Thus, this simple term, "restful sleep" implies an overall image of vitality that describes the healthy cycle of vigorous activity and restorative sleep. Ashwagandha is known for its neurocognitive benefits including nervous system restoration.[30-38]

Studies demonstrate that Ashwagandha benefits cognition and offers significant brain- and neuro-protective qualities. One study found 80% reduction in cell degeneration in the brain of stressed animals.[33] Another discussed the ability of an isolate of Ashwagandha to positively influence regeneration of neurons and synapses in damaged neurons and neural circuits – vital components of the nervous system and brain.[34,35] Ashwagandha may be protective of brain cells and support healthy brain function in degenerative brain conditions.[36] It is found to increase acetylcholine receptor activity, which may partially explain its ability to enhance cognition and memory.[37]

Uplift features KSM-66 Ashwagandha, a branded, full-spectrum extract made exclusively from the roots of the plant. It is produced using a unique proprietary extraction process and it has an extensive set of research studies and clinical trials. The efficacy of KSM® Ashwagandha extract in improving memory and cognitive function was studied. After eight weeks of study, the ashwagandha treatment group demonstrated significant improvements compared with the placebo group in both immediate and general memory. The treatment group also demonstrated significantly greater improvement in executive function, sustained attention, and information-processing speed, demonstrating that Ashwagandha may be effective in enhancing both immediate and general memory as well as improving executive function, attention, and information processing speed.[38]

For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please email info@naturaedu.com.

References

1. http://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml
2. Farahani MS, Bahramsoltani R, Farzaei MH, et al. *Plant-derived natural medicines for the management of depression: an overview of mechanisms of action*. Rev Neurosci 2015 26(3):305-21. doi: 10.1515/revneuro-2014-0058
3. http://www.nimh.nih.gov/health/topics/depression/index.shtml
4. Pratt LA, Brody DJ, Gu Q. *Antidepressant use in persons aged 12 and over: United States, 2005–2008*. NCHS data brief, no 76. Hyattsville, MD: National Center for Health Statistics. 2011. http://www.cdc.gov/nchs/data/databriefs/db76.htm
5. Muszy□ska B, Łojewski M, Rojowski J, et al. *Natural products of relevance in the prevention and supportive treatment of depression*. Psychiatr Pol 2015 May-Jun: 49(3):435-53. doi: 10.12740/PP/29367.
6. Parker G, Brotchie H. *Clinical overview: Mood effects of the amino acids tryptophan and tyrosine*. Acta Psychiatr Scand 2011: 124: 417–426. DOI: 10.1111/j.1600-0447.2011.01706.x
7. Gelenberg AJ, Wojcik, JD, Growdon, JH, et al. *Tyrosine for the treatment of depression*. Am J Psychiat 1980. 137:622–623.

Vitamins B6, Folate, B12

8. Elias MF, Sullivan LM, D'Agostino RB, et al. *Homocysteine and cognitive performance in the Framingham offspring study: age is important*. Am J Epidemiol 2005. Oct 1:162(7):644-53. Epub 2005 Aug 17.
9. Bourre, JM. *The role of nutritional factors on the structure and function of the brain: an update on dietary requirements*. Rev Neurol (Paris) 2004 Sep:160(8-9):767-92.
10. Tettamanti M, Garri MT, Nobili A, et al. *Low folate and the risk of cognitive and functional deficits in the very old: the Monzino 80-plus study*. J Am Coll Nutr 2006. Dec:25(6):502-8.
11. Vogiatzoglou A, Refsum H, Johnston C, et al. *Vitamin B12 status and rate of brain volume loss in community-dwelling elderly*. Neurology 2008. Sep 9:71(11):826-32.

Tyrosine

12. Neri DF, Wiegmann D, Stanny RR, et al. *The effects of tyrosine on cognitive performance during extended wakefulness*. Aviat Space Environ Med 1995. 313–9.
13. Gelenberg AJ, Wojcik JD, Falk WE, et al.*Tyrosine for depression: a double-blind trial*. J Affect Disord 1990. 19:125-32
14. Jongkees BJ, Hommel B, et al. *Effect of tyrosine supplementation on clinical and healthy populations under stress or cognitive demands-A review*. J Psychiatr Res 2015. Nov 70:50-7. doi: 10.1016/j.jpsychires.2015.08.014. Epub 2015 Aug 25.
15. Steenbergen L, Sellaro R, et al. *Tyrosine promotes cognitive flexibility: evidence from proactive vs. reactive control during task switching performance*. Neuropsychologia 2015. Mar. 69:50-5. doi: 10.1016/j.neuropsychologia.2015.01.022. Epub 2015 Jan 16.

St. John's Wort

16. Kasper S, Caraci F, Forti B, et al. *Efficacy and tolerability of Hypericum extract for the treatment of mild to moderate depression*. Eur Neuropsychopharmacol 2010. Nov 20(11):747-65. Epub 2010 Aug 14.
17. Butterweck V. *Mechanism of action of St John's wort in depression : what is known?* CNS Drugs 2003. 17(8):539-62.
18. Linde K, Berner MM, Kriston L. *St John's wort for major depression*. Cochrane Database Syst Rev 2008. Oct 8:(4):CD000448.
19. Kasper S. *Phytopharmaceutical treatment of anxiety, depression, and dementia in the elderly: evidence from randomized, controlled clinical trials*. Wien Med Wochenschr 2015. Jun 165(11-12):217-28. doi: 10.1007/s10354-015-0360-y. Epub 2015 Jun 20.
20. Nathan PJ. *Hypericum perforatum (St John's Wort): a non-selective reuptake inhibitor? A review of the recent advances in its pharmacology*. J Psychopharmacol. 2001 Mar:15(1):47-54.
21. Murch SJ, KrishnaRaj S, Saxena PK. *Tryptophan is a precursor for melatonin and serotonin biosynthesis in in vitro regenerated St. John's wort (Hypericum perforatum L. cv. Anthos) plants*. Plant Cell Reports 2000. 19:698-704.

Magnolia

22. Xu Q, Yi LT, Pan Y, et al. *Antidepressant-like effects of the mixture of honokiol and magnolol from the barks of Magnolia officinalis in stressed rodents*. Prog Neuropsychopharmacol Biol Psychiatry 2007. Nov 28.
23. Neri DF, Wiegmann D, Stanny RR, et al. *The effects of tyrosine on cognitive performance during extended wakefulness*. Aviat Space Environ Med 1995. 313–9.
24. Liou KT, Shen YC, Chen CF, et al. *Honokiol protects rat brain from focal cerebral ischemia-reperfusion injury by inhibiting neutrophil infiltration and reactive oxygen species production*. Brain Res 2003. Dec 5. 992(2):159-66.
25. Alexeev M, Grosenbaugh DK, et al. *The natural products magnolol and honokiol are positive allosteric modulators of both synaptic and extra-synaptic GABA(A) receptors*. Neuropharmacology 2012. Jun. 62(8):2507-14. doi: 10.1016/j.neuropharm.2012.03.002. Epub 2012 Mar 12.
26. Xu Q, Yi LT, Pan Y, et al. *Antidepressant-like effects of the mixture of honokiol and magnolol from the barks of Magnolia officinalis in stressed rodents*. Prog Neuropsychopharmacol Biol Psychiatry 2007. Nov 28.
27. Hou YC, Chao PD, Chen SY. *Honokiol and magnolol increased hippocampal acetylcholine release in freely-moving rats*. Am J Chin Med 2000. 28(3-4):379-84.
28. Ai J, Wang X, Nielsen M. *Honokiol and magnolol selectively interact with GABAA receptor subtypes in vitro*. Pharmacology 2001. Jul 63(1):34-41.

Tryptophan

29. Sandyk R. *L-tryptophan in neuropsychiatric disorders: a review*. Int J Neurosci 1992. Nov-Dec 67(1-4):127-44.

Ashwagandha

30. Jain S, Shukla SD, Sharma K, Bhatnagar M. *Neuroprotective effects of Withania somnifera* Dunn. in hippocampal sub-regions of female albino rat. Phytother Res 2001:15(6):544-8.
31. Bhattacharya SK, et al. *Anti-Stress activity of Sitoindosides VII and VIII, New Acylsteryglucosides from Withania somnifera.* Phytotherapy

Research 1987:1(1):32-37.

32. Archana R, Namasivayam A. *Antistressor effect of Withania somnifera.* J Ethnopharmacol 1999: Jan 64(1):91-3.
33. Jain S, Shukla SD, Sharma K, Bhatnagar M. *Neuroprotective effects of Withania somnifera* Dunn. in hippocampal sub-regions of female albino rat. Phytother Res 2001: 15(6):544-8.
34. Kuboyama T, Tohda C, Komatsu K. *Neuritic regeneration and synaptic reconstruction induced by withanolide* A. Br J Pharmacol 2005 Feb 14.
35. Tohda C, Kuboyama T, Komatsu K, Vanella A. *Indian medicinal plants as antiradicals and DNA cleavage protectors.* Phytomedicine 2001 Mar 8 (2):125-32.
36. Jayaprakasam B, Padmanabhan K, Nair MG. *Withanamides in Withania somnifera fruit protect PC-12 cells from beta-amyloid responsible for Alzheimer's disease.* Phytother Res. 2009 Dec 2.
37. Bhattacharya SK, Bhattacharya A, Sairam K, Ghosal S. Anxiolytic-antidepressant activity of Withania somnifera glycowithanolides: an experimental study. Phytomedicine Dec 2000: 7(6):463-9.
38. Efficacy and Safety of Ashwagandha (Withania somnifera (L.) Dunal) Root Extract in Improving Memory and Cognitive Functions Choudhary, D., Bhattacharyya, S., & Bose, S. (2017). Journal of Dietary Supplements, 1-14. Chicago